COMMENTS ON
42 CFR PART 73, INTERIM FINAL RULE
POSSESSION, USE AND TRANSFER OF SELECT AGENTS AND TOXINS

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Office of Laboratory Safety
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§ 73.1 Definitions.

We recommend including a definition for "Responsible Official."

We recommend using the USDA definition for Responsible Official, which reads, "The individual designated by an entity to act on its behalf. This individual must have the authority and control to ensure compliance with the regulations in this Part."

We recommend including a definition for "access."

Without a definition of the meaning of access, it is difficult to judge the potential impact and burden of the security, training, and record keeping requirements. The term "access" is used in the regulation to mean both access to select agents and toxins by individuals who are authorized to handle and use them, and approved entry to an area where select agents and toxins are present by individuals who are not authorized to handle or use select agents and toxins. We recommend defining access as "The ability to gain physical control of select agents and toxins." In this context, only those individuals who are authorized to handle and use select agents and toxins are considered to have access. In addition, we recommend use of the term "entry" rather than "access" when a requirement addresses access to an area where select agents and toxins are present.

§ 73.4 HHS Select Agents and Toxins.

We recommend deletion of Cercopithecine herpesvirus 1 (CHV-1) from the HHS list of select agents and toxins.

We do not agree that there is sufficient risk of infection by the aerosol route to warrant designating CHV-1 as a select agent. The agent summary for CHV-1 in the 4th Edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL) published in 1999, reads "Experimental work with animals indicates that the importance of aerosol exposure to CHV-1 is likely to be minimal." The 1997 National Research Council report, Occupational Health and Safety in the Care and Use of Research Animals, concludes, "The transmission of B virus by the aerosol route is not thought to be important."

One study on aerosol transmission of B virus in primates is in the literature (Chappell, W.A. "Animal Infectivity of Aerosols of Monkey B Virus." Annals of the New York Academy of Sciences. v. 85. p.931-34. 1960.) This study involved whole-body exposure to an aerosol cloud produced by an atomizer from a virus pool with a concentration of approximately 100 million tissue culture doses (TCD) per ml. Six Macaques were exposed. Four Macaques exposed to calculated inhalation doses of 250, 13,000, 13,000, and 25,000 TCD_{50},

respectively, showed no signs of illness. Two animals died—one five days after exposure to a calculated inhalation dose of 13,000 TCD_{50} and one eight days after exposure to a calculated inhalation dose of 50,000 $TCD_{50.}$ These doses are large and only likely achieved in the artificial environment of an experimental system. Whole-body exposures also create multiple routes of exposure such as mucous membranes, skin, and eye, which can contribute to disease. While this study demonstrates that significant exposures to CHV-1 may cause disease by the aerosol route, the risk of disease transmission by the aerosol route is low.

Macagues are widely used in research. Macagues are the natural host for CHV-1 and research shows that latent infection with this virus often occurs in these animals and their tissues. The 4th edition of the BMBL reports that approximately 50 human infections among animal care and laboratory personnel have occurred, resulting in 29 deaths of which 17 occurred before 1970. There is no documentation of the actual cause of infection in most cases. The only documented causative events involved bites and scratches by latently infected animals, cuts by contaminated glassware, or direct exposures to mucous membranes or the eye. There is no documented infection due to aerosol exposure. This experience is not consistent with an agent that presents a high risk of infection by the aerosol route—it is consistent with a conclusion that CHV-1 does not present a sufficient risk of infection by the aerosol route to warrant designation as a select agent.

We recommend that 42 CFR Part 73 include a summary of the risk assessment data that supports the listing of each select agent and toxin as an Appendix to the regulation.

These data will heighten the awareness of individuals who possess and use a listed agent to the most important risk characteristics of the listed agents. This knowledge will promote safe practices and proficiency in the handling of a listed agent.

§ 73.7 Registration.

§ 73.7 (b) (2) (viii).

We recommend deleting this provision from the Final Rule.

The last sentence of § 73.7 (e) covers the possible need for further inquiry or inspection.

§ 73.7 (c).

We recommend that HHS and USDA create a single office to receive all registrations for possession, use, and transfer of select agents and toxins covered by the requirements of 42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121.

The requirement to register with one or both HHS, CDC and USDA, APHIS is burdensome and inefficient. One registration office and reporting process would decrease regulatory burden, increase efficiency, ensure consistency in the application process and the guidance that is provided to assist entities in preparing acceptable applications, and ultimately promote compliance.

§ 73.7 (d).

We recommend deleting the word "protocol" from the third sentence in this provision and revising the sentence to read, "This includes modifications to the list of individuals approved under § 73.8, and changes in biosafety and laboratory information and objectives of the work with select agents or toxins."

This proposed language is consistent with information requested in the draft application for registration document, which does not seek information on protocols. Protocols can change frequently in active research programs without altering the relevant biosafety and laboratory information or the objectives of the work. A requirement for prior approval from HHS to modify a protocol before implementing the protocol change will predictably hinder research.

§ 73.7 (f).

We recommend that an entity have the option to apply for a single certificate of registration to cover activities at all buildings on a campus or site under the control and authority of the Responsible Official.

This would include both contiguous and dispersed sites within a local geographical area. Separate registrations for each general physical location (defined as "a building or a complex of buildings at a single mailing address") is overly burdensome in terms of staffing, training, and naming of Responsible Officials, and record keeping. § 73.9 Responsible Official, authorizes the Responsible Official to identify one or more Alternate Responsible Officials to provide coverage for and assist the Responsible Official. This nullifies the argument that separate registrations are necessary to ensure against over-extending the Responsible Official. In addition, administrative and control functions at research and academic institutions, including environmental health and safety and security programs, are efficiently managed by a centralized department responsible for more than one physical location.

§ 73.7 (g).

We recommend that the certificate of registration be valid for up to five years.

The change would make this provision consistent with § 73.8 (f), which sets a five-year expiration on the security risk assessment. This change would simplify paperwork logistics for the entity and reduce the cost to the government for the registration process.

§ 73.8 Security Risk Assessment.

Comment: The process for determining whether an individual is a "restricted person" or is a person to whom access to select agents and toxins should be denied by the HHS Secretary has the potential to prevent the HHS Secretary from satisfying a basic requirement of the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002." That requirement is to ensure the appropriate availability of biological agents and toxins for research, education, and other legitimate purposes. The process may result in constraining or stopping research by precluding or delaying researchers access to select agents and toxins. The Interim Final Rule does not describe the information the entity needs to submit to the

Attorney General or how to submit this information. It is unlikely that an entity can provide information for a security risk assessment, other than the name of an individual, since many institutions have privacy policies that preclude their seeking certain personal information. Institutions are also subject to state laws on privacy, which vary widely. In addition, the absence of an appeals or exemption process is troubling given the possible inaccuracies in the information contained in the databases that are available to the Federal Government and others. For example, it is predictable that some individuals who are currently productive, respected members of the scientific community and who have performed work with select agents or toxins meet one or more of the definitions of "restricted person." The Final Rule should provide provisions for entities and individuals to appeal security determinations or seek exemptions for legitimate research.

§ 73.8 (c).

We recommend that the Final Rule define the information the entity must submit to the Attorney General for the security risk assessment.

§ 73.8 (e).

We recommend that the Final Rule provide provisions for an entity or individual to appeal a security determination or seek an exemption allowing conditional access to select agents and toxins.

§ 73.8 (f).

We recommend that the HHS Secretary's approval for an individual to access select agents and toxins be portable from entity to entity, from location to location, and from project to project for the duration of the valid period.

§ 73.9 Responsible Official.

§ 73.9 (b).

We recommend adding to the end of this provision, "This does not preclude the assignment of activities in § 73.9 (c) (1) through § 73.9 (c) (7) to other individuals, provided the activities are performed or supervised by a person approved under § 73.8 and the results are reviewed and approved by the Responsible Official or Alternate Responsible Official."

§ 73.9 (b) implies that only the Responsible Official or Alternate Responsible Official may perform the tasks detailed in § 73.9 (c). It would be inappropriate to require these officials, for example, to participate in the actual transferring of a select agent or toxin, or to perform data entry to maintain records.

§ 73.10 Safety.

We recommend that the HHS Secretary not incorporate the Biosafety in Microbiological and Biomedical Laboratories and the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) as requirements in the Final Rule. We recommend that the Final Rule recognize these guidelines as authoritative codes of practice that entities should consider in developing and implementing a performance-based safety plan for the safe possession and use of select agents. In addition, the Final Rule should reference the performance-based OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, as the regulatory requirement for possession and use of toxins.

The safety provisions in the Interim Final Rule provide an acceptable approach for developing and managing a performance-based program for handling and containing select agents and toxins that will protect the safety of laboratory workers, the public, and the environment. This approach is valid because it requires an entity to consider the guidance provided in Biosafety in Microbiological and Biomedical Laboratories and the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) in developing compliant programs. These publications are recognized as authoritative codes of practice that reflect the best judgment of experienced and knowledgeable scientists, clinical microbiologists, and health and safety professionals on how to protect the safety of laboratory workers and the public health. These publications emphasize the importance of conducting a risk assessment before starting a new research program involving infectious agents and stress that such assessments may result in the selection of a combination of safeguards that necessarily differ from those listed under a specific biosafety level. These publications remain current with advancements in science through the support and encouragement of CDC and NIH to publish revisions periodically. Incorporating these guidelines as prescriptive requirements in the Final Rule would compromise their value and intent, and weaken the concept of a code of practice embraced by scientists, and health and safety professionals. The guidelines would soon lose current relevance because revisions would require rulemaking, which is a time-consuming and costly process.

As an example, the codification of the ACGIH's TLVs as PELs under OSHA's 29 CFR Part 1910 subpart Z Rule led to disparities between the OSHA Rule and revised guidance of ACGIH resulting from new findings. Codifying the HHS guidelines as prescriptive requirements in the 42 CFR Part 73 Final Rule would result in similar disparities because the conduct of science will undoubtedly move at a more rapid pace than rulemaking can sustain. In addition, OSHA has referenced authoritative guidance documents in its regulations. OSHA used this approach in the OSHA Laboratory Standard 29 CFR Part 1910, §1910.1450 to aid compliance, which is the Rule the HHS Interim Final Rule considers appropriate for handling toxins. In this OSHA Rule, a non-mandatory Appendix was included to provide guidance from the National Research Council's report, Prudent Practices for Handling Hazardous Chemicals in Laboratories.

§ 73.10 (d).

Comment: We agree that it is appropriate to reserve a section in the Final Rule for future specification of additional types of experiments that warrant stringent scrutiny in the interest of safety. Such experiments should require careful review by scientists recognized by their

peers as experts in the particular scientific area, and by health and safety professionals knowledgeable in risk assessment and laboratory safety before listing. We are aware that a committee of the National Research Council is currently considering such experiments. Results of this effort will be available in spring or early summer of 2003. In addition, the NIH Recombinant DNA Advisory Committee has a duty under the NIH Guidelines to assess the risks of potentially dangerous experiments involving recombinant DNA molecules. This Committee is able to provide valuable guidance on experiments that may warrant stringent scrutiny in the interest of safety.

We recommend that the CDC provide the comments it receives on 42 CFR Part 73, § 73.10 (d) to the National Research Council and the NIH Recombinant DNA Advisory Committee for their consideration. The CDC should not list new experiments in § 73.10 (d) without broad scientific review and guidance.

Individual scientists and Responsible Officials should also be alert to certain experiments that might warrant enhanced scrutiny, require increased control and containment levels, and or require cessation of research until the HHS Secretary has made a recommendation regarding appropriate safety practices. This information should come to the attention of peers, the Responsible Official, entity, or the HHS Secretary as appropriate.

§ 73.11 Security

Comment: This provision is not consistent with the performance-based approach used to establish requirements in other provisions of the Interim Final Rule. In addition, the MMWR article, "Laboratory Security and Emergency Response Guidance for Laboratories Working with Select Agents," which is meant to assist Responsible Officials "in meeting the regulatory mandate" of this provision, suggests the need for a rigorous security program applicable uniformly to all biosafety levels. This article also recommends that the first step in developing a compliant security program is to conduct a threat assessment and references a United States General Accounting Office (GAO) report on "Combating Terrorism: Threat and Risk Assessments Can Help Prioritize and Target Program Investments" for guidance. The GAO report explores the value to cities of the use of threat assessments to plan emergency response programs to deal with domestic terrorist incidents involving weapons of mass destruction. While Responsible Officials can extract useful material from this report, in whole, the report has little relevance to the security of select agents and toxins in teaching, diagnostic, and research laboratories. The security provisions should address specifically the development and implementation of a security program that will prevent unauthorized entry to biocontainment areas where select agents and toxins are present, and prevent unauthorized removal of select agents and toxins from these areas. The prescriptive requirements of this provision and lack of practical relevance of the primary cited guidance reference will impede the development of effective and affordable security plans and will result in constraining the availability of select agents and toxins for the legitimate purposes specified in the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002."

The Congress recognized that some select agents might pose a greater threat to the public health and safety than others. Accordingly, the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002" reads that the security requirements must be

"commensurate with the risk such agent or toxin poses to public health and safety (including the risk of use in domestic or international terrorism)." The HHS Secretary, therefore, has the flexibility to impose different levels of security requirements on different select agents and toxins based on an evaluation of the level of threat to the public, as is currently done with respect to laboratory biosafety levels. There are three primary characteristics of select agents and toxins that can help determine an appropriate level of security on the basis of risk to public health and safety: (1) case fatality rate; (2) contagiousness (ease of person-to-person transmission); and (3) presence of a natural reservoir in the United States. Less restrictive security measures are appropriate for select agents and toxins that cause disease having a low fatality rate, are non-contagious, and are present in the soil or in animals within the United States. Select agents requiring less restrictive security measures would include most of the select agents for which BMBL recommends Biosafety level 2 or 3 as appropriate for protecting laboratory workers and the public health.

We recommend that the security provisions provide performance-based requirements consistent with the approach used to establish the requirements for the safety provisions in 42 CFR Part 73. This approach should convey the appropriateness of establishing a tiered system of security controls that is commensurate with the risk such agent or toxin poses to public health and safety (including the risk of use in domestic or international terrorism).

§ 73.11 (a).

We recommend revising provision (a) to read, "The entity subject to the provisions of this Part must develop and implement a security plan. In developing the plan, an entity should consider a system of security controls that is commensurate with the risk such agent or toxin poses to public health and safety (including the risk of use in domestic or international terrorism)."

This revision incorporates the same performance-based approach used to establish the required safety plan and eliminates the perception of the need for a rigorous analysis more appropriate for American cities and international corporations in developing preparations for responding to attacks involving mass weapons of destruction.

§ 73.11 (b), (d), (e), and (f)

We recommend revising provisions (b), (d), (e) and (f) and consolidating these four provisions into a revised provision (b) to read:

(b) The security plan must address the following:
- **(1) Inventory control procedures;**
- **(2) Methods and procedures for maintaining physical security when individuals approved under § 73.8 are either present or are not present;**
- **(3) Procedures for allowing unapproved employees, service contactors, and guest workers under paragraph § 73.8 to enter and work in areas authorized for use or storage of select agents and toxins;**
- **(4) Procedures for reporting any compromise to the methods and procedures for maintaining physical security, including loss or theft of select agents or toxins, and entry into secure areas by unauthorized individuals;**

(5) Procedures for correcting any compromise to the methods and procedures for maintaining physical security;
(6) Security training for individuals authorized under § 73.8 and individuals approved by the entity to enter areas of use and storage;
(7) Procedures for receiving and transferring packages of select agents including the inspection of shipping containers for containment integrity; and
(8) Procedures for terminating use of select agents by the entity or by an individual authorized under § 73.8.

In addition to establishing a performance-based approach for developing and implementing a security plan, these recommendations eliminate the prescriptive provisions in this Part that would hinder collaboration among scientists such as provisions § 73.11 (d) (1) and (3). A productive research program likely includes many scientists and technicians working collaboratively but with only a few actually handling infectious agents. Isolating scientists who handle infectious agents will be detrimental to the program. The security requirements must enable unauthorized individuals to work together within the same physical space with scientists authorized under § 73.8.

§ 73.12 Emergency Response.

§ 73.12 (a).

We recommend revising the first sentence of this provision to read, "An entity subject to the provisions of this Part, must develop and implement an emergency plan that meets the applicable requirements of the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, and the OSHA Emergency Action Plans Standard, 29 CFR Part 1910, §1910.38."

Work conducted with hazardous materials in academic and research institutions is appropriately governed by the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, not by the OSHA Hazardous Waste Operations and Emergency Response Standard, 29 CFR Part 1910, §1910.120, which provides oversight of large scale hazardous materials spill response and remediation. Chemical Hygiene Plans, developed in accordance with the OSHA Laboratory Standard, 29 CFR Part 1910, §1910.1450, address laboratory-scale spill and release procedures. The OSHA Emergency Action Plans Standard, 29 CFR Part 1910, §1910.38 more appropriately addresses an institution-wide emergency response plan.

§ 73.13 Training.

§ 73.13 (a).

We recommend revising this provision in its entirety to read, "An entity required to register under this Part must provide information and training on safety and security for working with select agents and toxins to each individual approved for access under § 73.8 and each unapproved individual working in or visiting areas where select agents and toxins are handled or stored. An entity may modify the training according to the needs of the individual, the work they will do and their potential exposure. The

training need not duplicate training provided under the OSHA Bloodborne Pathogen Standard 29 CFR Part 1910, §1910.1030."

This revision makes clear the reference to the Bloodborne Pathogen Standard. In addition, the revision deletes the second sentence of the interim provision because § 73.13 (e) addresses this requirement.

§ 73.17 Notification for Theft, Loss, or Release.

§ 73.17 (d)

We recommend revising the first sentence of this provision to read, "The entity shall immediately notify the HHS Secretary and State and local public health agencies of any release of a select agent or toxin causing occupational exposure or release outside of the biocontainment area of a registered entity."

This change makes the provision consistent with the intent and language of the notification requirement in the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002." It also recognizes that compliant entities will confine work with select agents and toxins within biocontainment areas with secondary barriers and have appropriate procedures for safely responding to and managing spills within the biocontainment areas of a facility. These measures are generally sufficient to prevent occupational exposures and releases to public areas of the facility or the environment. Immediate reporting of a manageable spill outside of a primary containment barrier would unnecessarily activate a major response. Such a reaction would be wasteful of resources, increase apprehension and fear, and serve no benefit public health.